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Infectious diseases in Iran: a bird's eye view

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Abstract

Thanks to improved health standards in Iran over the past three decades, we have witnessed a shift in the causes of death in Iran from infectious causes to non-communicable diseases—mainly cardiovascular disorders, cancers, and road traffic injuries. The incidence and prevalence of many infectious diseases, such as many parasitic infections, have fallen significantly; there have been no reported cases of dracunculiasis in Iran since the mid-1970s. Great strides have also been made towards the elimination of schistosomiasis in Iran. However, we still have some problems with cutaneous leishmaniasis, hepatitis C, human immunodeficiency virus, tuberculosis, infections among immunocompromised hosts, hospital-acquired infections, and antibiotic-resistant bacterial strains. We need to emphasize improvements in sanitation, good clinical practice, and education about the rational administration of antibiotics.

Keywords: Bacterial infections, communicable diseases, drug resistance, epidemiology, incidence, infection control, microbial, parasitic diseases, prevalence, viral diseases

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Introduction

Infectious diseases constitute a major healthcare burden for many developing countries. Despite all of the efforts made to control infectious diseases, it is estimated that, by the year 2025, they will still kill almost 5 000 000 children under 5 years of age, mostly in developing countries [1].

Iran, a country with an area of 1 648 000 km^2 in the Middle East, with its various climates, suffers from a wide array of infectious diseases. Previously, the diseases were responsible for most deaths in Iran [2]; however, thanks to improved health standards and the establishment of national surveillance systems over the past two decades, we have witnessed a shift in the causes of death in Iran from infectious causes to non-communicable diseases—mainly cardiovascular disorders, cancers, and road traffic injuries [2,3]. Herein, we wish to present a bird's eye view of common and important infectious diseases in Iran.

Viral Infections

Viral hepatitis

Viral hepatitis is more common in Iran than in western countries. Hepatitis A and B viruses are the most common causes of acute hepatitis in children and adults, respectively. The prevalence of hepatitis A in Iran, as in many countries in the region, is very high, and although the age of exposure to the virus has been increasing in Iran, owing to improved sanitary measures, children and young adults remain the primary targets, so that most children in Iran contract the disease and have immunity by the age of 10 years. In most parts of

Iran, >90% of people aged ≥33 years are seropositive for anti-hepatitis A virus antibody [4–8].

Hepatitis B virus is the most common cause of acute hepatitis in adults. We have witnessed a dramatic decline in the prevalence of hepatitis B in Iran during the last decade; the country is now classified as a region with 'intermediate prevalence' for the disease [9]. Increased popular awareness of hepatitis B risk factors and the establishment of a national hepatitis B vaccination programme in 1993, which includes vaccination of all neonates and vaccination of high-risk groups, could be the reasons for this change. The overall prevalence of hepatitis B surface antigen in Iran is 2.1%. Prevalence rates of >3% are reported in north-eastern Iran; the rate decreases to <2% in the central and western regions [10]. It was shown that genotype D was the only type found in all hepatitis B surface antigen-positive patients [11,12]. The vaccination programme has significantly decreased the carrier rate among young children. As a consequence, the average age of infected people has increased [9].

In Iran, predictors of hepatitis B included family history of the infection, history of receiving blood transfusion, hospitalization, unsafe sex, male gender, and living in urban areas [9]. History of surgery and imprisonment were other major risk factors for infection [5,13]. Certain jobs [14–16] and ethnicities [17] carry a higher risk of acquisition of the infection. Approximately 1.5 million people in Iran are living with the infection; it is estimated that 15–40% of these people are at risk of developing cirrhosis and hepatocellular carcinoma, if left untreated [10,18]. Hepatitis B virus is therefore a true heathcare burden for Iran.

The overall prevalence of hepatitis C in Iran is <1% [5,19], but the rate is much higher among multiply transfused patients [20], including those with β-thalassaemia major [21–23] or coagulopathy [24], and patients with end-stage renal disease undergoing chronic haemodialysis [25,26]. Hepatitis C virus is the aetiology of <10% of cases of chronic hepatitis or liver cirrhosis. The pooled estimate of the prevalence of hepatitis C in haemodialysis patients in Iran is 16%, with a minimum of 3% in Isfahan province (central Iran) to a maximum of 28% in Golestan province (north-eastern Iran) [25]. The prevalence of the infection is also high among intravenous drug users [19,27], but the rate has decreased with the expansion of services for them, such as needle and syringe programmes [28].

Hepatitis C virus infection is common in kidney transplant recipients. It is a major cause of chronic liver disease following renal transplantation, and is associated with higher morbidity and mortality rates in patients on chronic haemodialysis [29]; it is also a major threat to allograft survival in renal transplant recipients [26]. Although not common in the general population, the infection imposes a great burden on Iran, because of its serious complications and the associated treatments.

Human immunodeficiency virus (HIV) infection

The prevalence of HIV infection in the 15–49-year-old age group increased from almost 0.02% in 1990 to 0.2% in 2004, after which the rate reached a plateau. There are almost 92 000 people living with HIV. Annually, 6000–6500 people die of AIDS [30]. The main cause of death in patients with HIV is tuberculosis [31]. Although patients have free access to antiretroviral therapy, their adherence to highly active antiretroviral therapy, one of the most commonly used drug regimens in Iran, does not exceed 70% [32]. One of the important routes of transmission in Iran is sharing of syringes by intravenous drug users. As HIV and hepatitis C virus are transmitted in the same way, co-infection with these two viruses is not uncommon. In a recent study from Shiraz, southern Iran, 78% of 1338 studied HIV-infected patients were also infected with hepatitis C virus, which increases the likelihood of AIDS-related deaths by more than two-fold [33]. Another report also showed high rates of co-infection with hepatitis B or C virus in HIV-infected patients in Iran [34]. The co-infection rates were significantly higher in intravenous drug users.

Crimean–Congo haemorrhagic fever (CCHF)

Considering the descriptions of a haemorrhagic syndrome associated with ticks in the book *Zakhyre Kharazmshahi* (Thesaurus of the Shah of Khwarazm) compiled by the Iranian scholar Jorjani, CCHF may have been reported in Iran as early as AD 1110 [35]. However, the first evidence of the disease in the country was presented by Chumakov *et al.*, in 1970, when 45% of sheep sent from a Tehran abattoir to Moscow tested positive for CCHF antigen [35]. The first confirmed human cases of CCHF in Iran were reported in 1974 and 1975 [36]. However, it was not until the 1999 outbreak that CCHF was recognized as an important public health problem in Iran. Between January 2000 and September 2010, 738 cases of CCHF and 108 deaths from the disease were reported in Iran [36,37]. During this period, the disease was reported from 23 provinces of Iran; the highest incidence rates, in descending order, were in Sistan-va-Baluchestan (south-eastern Iran), Isfahan (central Iran), Fars (southern Iran), Khorasan (north-eastern Iran), and Tehran (northern Iran). The virus isolated from Iranian patients had the same phylogenetic characteristic as that isolated from Pakistan (CCHF Matin strain) [38]. The maximum reported incidence of CCHF was in 2002 [39]. However, as CCHF presents with non-specific influenza-like symptoms, its diagnosis can be difficult. The disease is usually transmitted by ticks, but person-to-person transmission through close

contact with patients or nosocomial transmission is not uncommon [39]. There are no important reports from Iran on other types of haemorrhagic fever.

Other emerging viral infections

A recent study of West Nile virus in the equine population in Iran reported an overall seroprevalence of 24% (range: 1–88%), with the highest values being observed in the southern and western parts of the country [40]. In another study, of 500 blood donors tested, 5% were found to be positive for IgG against the virus; no one tested positive for IgM [41]. In Iran, the prevalence of West Nile virus is low in patients with encephalitis [42]. There is no information from Iran on other emerging infections, such as Chikungunya fever, dengue fever, Rift Valley fever, and hantavirus infections.

Bacterial Infections

Tuberculosis

Tuberculosis was once well controlled in Iran, but, owing to the recurrence of the disease, the appearance of drug-resistant strains, and the association of tuberculosis with the HIV pandemic (as in many parts of the world), it is becoming a problem for Iran too. The incidence of tuberculosis in Iran is 17/100 000 population, and its prevalence is 23/100 000 population. It has a mortality rate of 1.8/100 000 people [43]. The distribution of the disease, however, is not uniform; the incidence and prevalence of tuberculosis are lower in the central parts, and higher in provinces near the country borders [44]. Co-infection with HIV is not uncommon; 27% of patients with tuberculosis are HIV-positive. Multidrug resistance is another important issue; 5% of new patients diagnosed with tuberculosis have multidrug-resistant tuberculosis (MDR-TB). Approximately 52% of patients are smear-positive, 16% are smear-negative, and 29% present with extrapulmonary involvement [43]. In a recent study, of 1742 patients with tuberculosis, 668 (38.3%) were Afghan refugees, and 263 (15.1%) patients had MDR-TB. Factors associated with MDR-TB included age <45 years, male sex, previous treatment for the disease, immigration, poor living conditions, and unemployment [45]. The high rate of initial resistance in patients with MDR-TB and the high incidence of MDR-TB in young patients could reflect recent transmission, which warrants closer monitoring of transmission trends in MDR-TB strains.

Brucellosis

Human brucellosis is endemic in all parts of Iran [46]. The annual incidence of the disease in Iran had fallen from >1000/1 000 000 population in 1989 to 238/1 000 000 in 2003 [47–49]. The disease is contracted mainly by drinking raw milk and eating soft goat cheese, and less frequently through abrasions of the skin, inhalation of infectious aerosols, or direct contact of contaminated materials with the conjunctiva. The disease is of particular importance for certain occupations, as these routes of the infection are more important for veterinarians, laboratory technicians, butchers, and farmers, who have direct contact with animals and their products, such as blood, meat, placenta, and fetuses [50]. Person-to-person transmission of the disease is rare. However, in cases of transmission, the most probable route is sexual contact. Many people in rural areas of Iran have close contact with domestic animals, and consume raw milk and soft cheese; many children work as shepherds, so brucellosis is endemic. Furthermore, in some rural areas in Iran, there is a belief that, for prevention of infection in newborns, they should be fed with raw colostrum, which is rich in the microorganisms if the sheep is infected. Therefore, in many rural areas, brucellosis is an endemic zoonotic disease in all age groups and both sexes. Brucellosis is still a burden for Iran, not only as a healthcare problem, but also because of the financial loss in livestock industries; the disease causes repeated abortions in most infected animals [50].

Enteropathogens

Escherichia coli, *Shigella* and *Salmonella* spp. are among the most important bacteria causing diarrhoea worldwide. In a study in Hamedan, in the north-west of Iran, of 144 samples collected from patients with acute diarrhoea, 11.8% were positive for *Shigella* strains, and 25.7% for *E. coli* (10.4% were Shiga toxin-producing *E. coli*); no *Salmonella* strains were isolated. In 9.7% of studied patients, there was co-infection [51]. In another study from Zahedan, Sistan-va-Baluchestan, south-eastern Iran, of 322 paediatric patients presenting with diarrhoea, only two (0.6%) were found to be infected with *E. coli* O157:H7 [52]. Another study from Gorgan, northern Iran, showed that 8.8% of samples taken from 634 patients with diarrhoea were positive for *Shigella* spp.; *Shigella sonnei* was the predominant species (55%), with the highest frequency in summer, mostly associated with abdominal pain and isolated from patients 2–5 years of age [53]. One study from Shiraz, southern Iran, showed that, of 114 samples collected from 2–58-year-old patients with diarrhoea, 9.6% were positive for *Campylobacter jejuni*, 15.8% for *Salmonella* spp., and 9.6% for *Shigella* spp. The highest prevalence of *C. jejuni* was observed in patients aged 11–15 years [54].

There are reports on the emergence of antibiotic-resistant enteropathogens. A recent study revealed that most of the

Shigella isolates in Bushehr, southern Iran, are no longer sensitive to tetracycline and co-trimoxazole [54]. In contrast to previous reports from Iran [55], which showed that all of the *Salmonella* Typhi isolates were pan-susceptible to the antibiotics used, a recent study revealed a high frequency of multidrug resistance in many *Salmonella* isolates recovered from patients admitted to six different hospitals in Tehran, northern Iran [56].

Helicobacter pylori

Helicobacter pylori has an important role in the pathophysiology of peptic ulcer disease and the development of gastric metaplasia and gastric cancer [57]. Therefore, the infection may impose an indirect heath burden in a country where gastric cancer is common. In Iran, the prevalence of infection is 40.9% in the 7–18-year age group, 68% in the 19–45-year age group, and 75.6% in the ≥45-year age group.

Chlamydial infection

The prevalence of chlamydial infection in north-eastern Iran is high; of 178 male patients presenting with urethritis in Mashhad, 10.7% were infected with *Chlamydia trachomatis* [58]. There is a high prevalence of *Chlamydia trachomatis* infection among women with cervicitis in Tehran; 49% of 31–40-year-old patients and 33% of 20–30-year-old patients were positive for the infection [59].

Leptospirosis

With an incidence rate of 1.6/100 000 people per year, leptospirosis is not uncommon in Mazandaran province, northern Iran, where rice cultivation fields are abundant [60]. The disease is mainly occupational [61], and is typically seen in 40–59-year-old male farmers during summer.

Q-fever

There is little information on human Q-fever in Iran. A recent study conducted in south-eastern Iran on febrile patients with suspected brucellosis reported *Coxiella burnetii* phase I and II specific IgG in 24% and 36% of patients, respectively [62]. Another study reported the first molecular detection of *Coxiella burnetii* in ticks collected from domestic animals in Kerman Province, south-eastern Iran [63].

Listeriosis

There is little information on the epidemiology of listeriosis in Iran. In a study conducted in 1989 in Teheran, 1–11% of children were found to be seropositive against one of different serotypes of *Listeria* [64]. A recent case–control study on women of child-bearing age revealed that 36% of those with a history of spontaneous abortion and 18% of those with normal full-term deliveries were positive for *Listeria monocytogenes* antibody [65].

Parasitic Infections

Over the last four decades, we have witnessed a significant fall in the prevalence rates of many helminthic infections in general, and of some of the intestinal nematodes in particular. For example, the prevalence of human ascariasis in Mazandaran province, northern Iran, fell from 86.3% in 1961 to merely 0.3% in 1995 [66,67]. The overall prevalence of *Ascaris lumbricoides* in Iran is 1.5%; the highest rate of >23% was reported from north-western regions. Hookworms have a low prevalence rate of <0.1% in Iran. *Trichostrongylus* has a pooled prevalence of 0.2%, with the highest rate reported from Khuzestan, in the north of the Persian Gulf. *Trichuris trichiura* and *Taenia saginata* have prevalence rates of 0.1% and 0.2%, respectively [68]. There have been no reported cases of dracunculiasis in Iran since the mid-1970s. Great strides have also been made towards the elimination of schistosomiasis in Iran [68,69]. However, some helminthic diseases, especially those with a direct faecal–oral route of transmission, such as that caused by *Enterobius vermicularis*, remain common in many parts of Iran. The reported prevalence of the disease ranges from 9% in the south-western region to 35% in Urmia, in the north-west [68]. In a nationwide survey of the prevalence of intestinal parasitic infections in Iran, of 53 995 people aged >2 years, 19.3% had intestinal parasitic infections. *Giardia lamblia* (10.9%), *A. lumbricoides* (1.5%), *Entamoeba histolytica* (1.0%) and *Enterobius vermicularis* (0.5%) were the most common parasites isolated [70]. The prevalence was highest in the 2–14-year-old age group (25.5%) and in rural areas (23.7%).

Giardiasis is the most common parasitic infection in Iran. In a national study, the pooled prevalence was 18.3% in the 2–14-year-old age group, 12.3% in the 15–39-year age group, and 9.7% in the 40–69-year age group [71]. The prevalence in rural areas (15.4%) was slightly higher than that in urban areas (13.7%). Males were more affected than females (15.1% vs. 13.9%) [71]. The peak prevalence was observed in boys aged 10–12 years and girls aged 8–10 years. In some cities in the Caspian littoral, northern Iran, the prevalence was 70% in males and 30% of females. In hyperendemic areas, the infection may even be observed in neonates [72].

Echinococcosis

Echinococcus granulosus is hyperendemic in Iran; the disease prevalence was increased by an influx of infected Afghan refugees. Between 5% and 50% of the stray or sheep dogs

studied in various parts of Iran were infected with adult *Echinococcus granulosus* [68,73,74]. In Iran, three distinct life cycles have been suggested: a domestic cycle between dogs and livestock, a desert cycle between dogs and camels, and a sylvatic cycle between wild carnivores and wild ruminants [74]. *Echinococcus multilocularis* is rare in Iran.

Fascioliasis

Two decades ago, fascioliasis was considered to be an important chronic disease in the Caspian littoral, northern Iran [68,75]. Between 1999 and 2002, 107 patients from this region were found to be infected with *Fasciola*. The infection has been linked to frequent ingestion of potentially contaminated aquatic plants. In 2000, there was also a report of 17 cases of non-fatal fascioliasis in the western province of Kermanshah [76]. The infection was found in 1.5% of the local cattle; the source of the human infections was believed to be consumption of contaminated watercress [76].

Leishmaniasis

The cutaneous form of the disease is the most common form of leishmaniasis in Iran [69]. Mucocutaneous leishmaniasis (espundia) is extremely rare in Iran [77]. However, there are foci of visceral leishmaniasis (kala-azar), mainly in southern and western parts of the country [78]. With the spread of HIV, the disease has become increasingly prevalent, and unusual presentations often occur [79]. The most common causes of the disease in Iran are *Leishmania tropica* and *Leishmania major* [80,81]. The vector for anthroponotic cutaneous leishmaniasis is *Phlebotomus sergenti*; for zoonotic cutaneous leishmaniasis, the vectors are *Phlebotomus papatasi* and *Phlebotomus caucasicus* [78].

Malaria

The high frequency of haemoglobinopathies in Iran is evidence for the existence of malaria in ancient times in Iran [82], but the country is now in the pre-elimination phase; according to a recent WHO report, there are 564 active foci of malaria in Iran. These foci are mainly in the southeastern parts of the country. More than 95% of all malaria patients live in these areas, including Sistan-va-Baluchestan province, Hormozgan province and tropical parts of Kerman province. Only 3% of Iranians live in these regions [83]. The annual incidence of malaria in Iran was estimated to be 0.14–8.74/1000 people in 2010 [84]. According to the WHO, there were almost 70 000 confirmed cases of malaria in Iran in 2010 [85]. The major *Plasmodium* spp. in Iran are *Plasmodium falciparum* and *Plasmodium vivax*; the most important vectors are *Anopheles stephensi*, *Anopheles culicifacies*, *Anopheles fluviatilis*, and *Anopheles superpictus* [83].

Nosocomial Infections

Hospital-acquired infections (HAIs) constitute one of the most important healthcare burdens in Iran, and are mostly preventable [86]. According to National Nosocomial Infections Surveillance data collected between 2007 and 2010 from 100 hospitals with >200 beds, among 6 616 520 studied patients, the most common HAIs were urinary tract infections (28.9%), pneumonia (28%), surgical site infections (26.8%), and bloodstream infections (16.4%). HAIs were most prevalent in burns wards, followed by intensive-care units, and haematology/oncology wards. The overall mortality rate among patients with HAIs was 14.8% [87].

In a recent study conducted in southern Iran on 3450 patients, the overall prevalence of HAIs was 9.4%; the most common HAIs were bloodstream infections (2.5%), surgical site infections (2.4%), urinary tract infections (1.4%), and pneumonia (1.3%) [88]. Use of a central intravenous catheter, having a urinary catheter and hospital stays of >8 days were independent risk factors for the development of HAIs. Being admitted to an intensive-care unit was not an independent risk factor for the development of HAIs. There was a high discrepancy between the development of HAIs and antibiotic use. Whereas 71% of the patients were treated with antibiotics, only 9.4% of them also had at least one documented infection [88]. Both the type of infection and the causative organism depend on the ward and the procedure performed. Whereas the most common HAI in patients admitted to an intensive-care unit was ventilator-associated pneumonia, mostly caused by *Acinetobacter baumannii*, *Staphylococcus aureus* (both methicillin-resistant and methicillin-sensitive), and *Pseudomonas aeruginosa* [89], the most common HAI in patients admitted for elective open-heart surgery was surgical site infection [90]. In another study on patients admitted to an intensive-care unit in northern Iran, urinary tract infection caused by *Klebsiella* spp. was the most common HAI [91].

With the introduction of transplantation and the increase in longevity of immunocompromised patients, one of the challenging problems is management of infection in these patients [92]. Invasive fungal infections, usually caused by *Aspergillus* spp., *Mucorales* spp., *Candida* spp., and *Cryptococcus neoformans*, are important causes of mortality in transplant patients in Iran [93].

Antibiotic Resistance

Another important health burden for Iran is antibiotic resistance, which is, in fact, a global health problem; the burden of antibiotic resistance is mainly borne by developing coun-

tries. Irrational use of antibiotics causes the development of resistant bacterial strains [94]. The three most commonly prescribed antibiotics in 2001 were amoxycillin, co-trimoxazole, and ampicillin [95]. Currently, the most commonly used antibiotics include cefixime, ceftriaxone, ciprofluoxacin, amoxycillin–clavulanic acid, and azithromycin. Iranian physicians, like many of those practising in the region, might prescribe antibiotics for the treatment of non-bacterial infections, such as viral infections, for which antibiotics are completely useless [94]. In Iran, the irrational use of antibiotics is not restricted to humans. Antibiotics are reportedly overused in veterinary medicine and the poultry and fishery industries too; this leads to the emergence of resistant microbial strains in animals, and the spread of such strains to people through the food chain [96].

The prevalence of antibiotic-resistant bacteria in Iran is high. In a recent study, 10.23% of >25 000 blood cultures examined over a period of 5 years were positive for bacterial growth, and 46.7% of the organisms were Gram-positive bacteria. Among the Gram-positive bacteria recovered, 79% were methicillin-resistant *S. aureus* [97]. Another study, conducted in a teaching hospital in Tabriz, north-western Iran, reported that 63% of *Acinetobacter baumannii* isolates collected from various clinical specimens were resistant to carbapenems, the antibiotics that are considered to be the last available line of defence against many Gram-negative bacteria [96,98]. Another study, in Ahwaz, south-western Iran, revealed that 38% of *P. aeruginosa* strains isolated from 100 burns patients were multidrug-resistant; 41% of the isolates were resistant to carbapenems [99]. There also reports of multidrug-resistant *Salmonella* spp. [56].

Islam is the prevailing religion in Iran. Every year, a large number of people from Iran go to Saudi Arabia to take part in the Hajj ritual, which is another important issue to be considered in the control of infectious diseases. In mass gatherings such as the Hajj, antibiotic-resistant strains can easily be spread to the region or other continents by international travellers. Every year after the return of pilgrims from the Hajj, physicians in Iran face several new infectious diseases—mainly flu-like syndromes [96,100].

Transparency Declaration

All authors declare no potential conflict of interest.

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